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EXAMINER

RAMIREZ, DELIA M

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 12/02/2002

21

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N .

09/291,347

Applicant(s)

HANAK ET AL.

Examiner

Delia M. Ramirez

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1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 September 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4-18 and 37 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4-18 and 37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Status of the Application

Claims 4-18 and 37 are pending.

Applicant's amendment of claims 4-7, 11-15, 18, 37, submission of a substitute specification, and a request for consideration in Paper No. 19, filed on 9/13/2002 are acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Specification

1. Applicant's submission of a substitute specification with corrections as requested in previous Office Action Paper No. 18 is sufficient to overcome the objection previously applied.

Priority

2. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/081726 filed on 4/14/1998.

3. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to UK application No. 9807922.1 filed on 4/14/1998 and UK application No. 9817151.5 filed on 8/6/1998.

Drawings

4. The formal drawings submitted on 9/13/2002 have been reviewed and are approved by a draftsman under 37 CFR 1.84 or 1.152.

Claim Rejections - 35 USC § 112, Second Paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 4-18 and 37 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Applicant's amendments to the claims and/or clarification as to where and how the terms "substantially RNA-free" and "non-specific RNase" have been defined in the specification, is deemed sufficient to overcome the previously applied rejections, which are hereby withdrawn.

Claim Rejections - 35 USC § 112, First Paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 4-18 and 37 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for preparing RNA-free cellular components in an *E. coli* cell, wherein the cellular component and RNaseI or RNaseA are produced by said *E.*

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coli cell and wherein RNaseI or RNaseA are expressed and secreted using an inducible or constitutive promoter, does not reasonably provide enablement for a method for preparing RNA-free cellular components wherein any RNase is expressed in any cell and wherein any RNase is expressed constitutively in the cytoplasm. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

10. This rejection has been discussed in previous Office Action Paper No. 18, mailed on 6/13/2002.

11. Applicant's argue that the specification in view of what is known in the art is enabling for practicing the claimed method with any known RNase. Applicants assert that it appears that the Examiner is placing the burden on Applicants to enable hypothetical or unknown RNases and request that art be cited to support the contention of lack of enablement for undisclosed RNases. Furthermore, it is Applicant's opinion that there is no need to provide what is well known in the art. It is Applicant's contention that the teachings of Okorokov et al. are at most unsupported speculations and that Zhu et al. teaches that "an alternate possibility is that any RNase I within the cell is in an inactive form. It is known that RNase I binds tightly to ribosomes in vitro and may do so in vivo". Applicants argue that while some experimentation may be useful, the key word is "undue".

12. It is noted that the claims 4-18 have been amended to limit the scope of the claims, which now recite "cells producing an RNase are microbial". Claim 37 is still directed to a method wherein the RNase can be produced by any type of cell.

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13. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. As indicated above, claim 37 is directed to a method wherein any cell can be used to express the RNase, however there is no information as to which promoters can be used in any cell to produce RNases. Also, the claims as written encompass a method for preparing RNA-free cellular components wherein the RNase and the cellular component are both produced by the same microbial cell in the cytoplasm. It is not clear how one of skill in the art would dismiss the teachings of Okorokov as "unsupported speculations" since one of ordinary skill in the art would expect degradation of essential RNA if RNase is overexpressed in the cytoplasm, due to the fact that RNases degrade RNA. Contrary to Applicant's assertion, the teachings of Zhu et al. further support the teachings of Okorokov et al. in view of (1) the admission by Zhu et al. that overexpression of RNase I without any deleterious effect on the cell was unexpected (page 3149, second column, last paragraph, Discussion), (2) the admission by Zhu et al. that in fact 85% of the RNase I activity was present in the periplasmic space and not in the cytoplasm (page 3149, second column, last paragraph), and (3) the admission by Zhu et al. that the remaining RNase which is in the cytoplasm may be inactive (page 3149, second column, last 4 lines, page 3150, first column, first five lines). Even Applicant's own specification teaches that to prevent toxic effects on the host cell, RNases should be expressed with signal peptides to direct them to the periplasmic space or the culture supernatant (page 34, paragraph 177 of substitute specification). In regard to Applicant's contention that the specification is enabling for practicing the claimed method with any RNase, while it is agreed that many RNases are known in the art, it is unclear if the use of specific RNases would also result in substantially RNA-free compositions as defined in the specification. The specification only discloses the use

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of non-specific RNases and no examples have been provided of the use of specific RNases to achieve the degree of RNA level desired. Thus, Applicants have not provided sufficient guidance to enable of skill in the art to use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 103

14. Claims 4, 6-7, 9-13, and 15-18 were rejected under 35 U.S.C. 103(a) as being unpatentable over McMaster et al. (Analytical Biochemistry 109:47-54, 1980; cited in the IDS) in view of Okorokov et al. (Protein Expression and Purification 6:472-480, 1995; cited in the specification).

15. This rejection has been discussed at length in Paper No. 18, mailed on 6/13/2002.

16. Applicants argue that there is no language, implicit or explicit, in the teachings of McMaster et al. or Okorokov et al. to combine the teachings of both references. Applicants assert that McMaster et al. teaches the addition of purified RNase and that the cell lysate of Okorokov et al. would contain contaminating DNases. It is Applicant's opinion that there is no teaching or suggestion in either of the references cited which would lead one of skill in the art to combine their teachings with a reasonable expectation of success.

17. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references

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themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, while one could argue that there is no motivation to combine the references since the presence of DNase can destroy the DNA being produced, McMaster et al. also teaches how to eliminate DNases. Therefore one would be motivated to use the RNase-containing lysate of Okorokov et al. since RNase A is well known and widely used in the art for purification of DNA from crude lysates and DNases can be inactivated by heating at 70 C. There is a reasonable expectation of success at inactivation of RNases and DNases since McMaster et al. teaches the use of RNase A to inactivate RNA in the plasmid DNA preparation and how to inactivate DNases. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

18. Claims 8 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over McMaster et al. (Analytical Biochemistry 109:47-54, 1980; cited in the IDS) in view of Okorokov et al. (Protein Expression and Purification 6:472-480, 1995; cited in the specification) as applied to claims 4 and 11 and further in view of Zhu et al. (J. Bacteriol. 172:3146-3151, 1990).

19. This rejection has been discussed at length in Paper No. 18, mailed on 6/13/2002.

20. Applicants argue that there is no reason to combine the teachings of the cited references for the same reasons discussed above and even if there were motivation, one of skill in the art would have been concerned with the presence of DNase contamination.

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21. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. For the reasons discussed above, one of skill in the art would have been motivated to combine the references and have a reasonable expectation of success. As indicated above, one of skill in the art could have inactivated the DNases in the cell lysate of Okorokov et al. as taught by McMaster et al. As discussed in previous Office Action Paper No. 18, one of skill in the art is motivated to constitutively express the RNase in the method of McMaster et al. and Okorokov et al. because there is no need for an inducer and to avoid plasmid instability. There is a reasonable expectation of success since Zhu et al. teaches the constitutive expression of RNase I in *E. coli* by inserting of DNA encoding RNase I in the chromosome. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

22. No claim is in condition for allowance.

23. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

24. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.


25. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
November 26, 2002


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1600